DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

APPLICATION FOR ESTABLISHMENT LICENSE FOR MANUFACTURE OF BIOLOGICAL PRODUCTS

Form Approved: OMB No. 0910-0124.
Expiration Date: November 30, 2001.
See Page 18 For OMB Statement.

DATE SUBMITTED

NOTE: This report is mandated by Section 351 of the Public Health Service Act, the Federal Food, Drug and Cosmetic Act, Section 502, and Title 21 CFR Part 600. No license may be granted unless this completed application form has been received.

GENERAL INSTRUCTIONS

Type or print legibly in ink. Complete all items. Items which are not applicable, enter "NA". If more space is needed for any item, continue on an 8 1/2 x 11 inch sheet, reference the entry by item number, and attach. Allow 1 inch top margin for filing purposes. Submit the original and yellow copies of the completed application. Assemble and staple each set, including all attachments. The application forms must be dated and signed by the responsible head. Return this application to DHHS/PHS, FDA/Director, Center for Biologics Evaluation and Research (HFM-370), 1401 Rockville Pike, Rockville, MD 20852-1448.

I. GENERAL INFORMATION

A. NAME AND ADDRESS OF MANUFACTURER FOR WHICH U.S. LICENSE IS BEING MADE INCLUDE A COPY OF THE CERTIFICATE OF INCORPORATION *(Without financial detai*

CHECK ONE:

☐ NEW APPLICATION

☐ REVISED APPLICATION

TELEPHONE NUMBER

( )

B. NAME, ADDRESS AND REGISTRATION NUMBER OF EACH LOCATION OF THE ESTABLISHMENT WHERE ACTUAL MANUFACTURING, INCLUDING TESTING, LABELING AND STORAGE, TAKES PLACE. IDENTIFY THE MANUFACTURING PERFORMED AT EACH LOCATION. IF THIS IS A SHARED OR CONTRACT MANUFACTURING ARRANGEMENT DESCRIBE THE FUNCTIONS PERFORMED AT EACH LOCATION.

C. NAME, ADDRESS AND PHONE NUMBER OF RESPONSIBLE INDIVIDUAL *(Responsible Head 21 CFR 600.10) TO* WHOM ALL OFFICIAL CORRESPONDENCE

D. NAME AND ADDRESS OF OTHER RESPONSIBLE OFFICIAL OR AGENT TO WHOM COPIES OF CORRESPONDENCE SHOULD BE

E. NAME OF INDIVIDUAL(S) DELEGATED RESPONSIBILITY FOR RELEASE PROTOCOL SIGN-OFF BY THE RESPONSIBLE HEAD *(If it is not the Responsible Head).*

F. A BRIEF DESCRIPTION OF THE PRODUCT OR PRODUCTS COVERED BY THIS APPLICATION. PLEASE INCLUDE A MANUFACTURING FLOW DIAGRAM INDICATING LOCATIONS WITHIN THE FACILITY WHERE EACH MANUFACTURING STEP IS PERFORMED.

I. GENERAL INFORMATION *(Cont'd)*

G. GENERAL OVERVIEW OF ALL MANUFACTURING LOCATIONS INCLUDING:

1. SITE PLAN
2. INDICATE IF THIS IS A MULTI PRODUCT FACILITY AND DESCRIBE ALL PRODUCTS *(Drugs, biologics, and medical devices or any combination)* MADE AT EACH SITE
3. OTHER NDUSTRY IN THE AREA
4. DISTANCE FROM FARM ANIMALS
5. SQUARE FOOTAGE
6. PEST CONTROL

H. PROVIDE FLOW DIAGRAMS FOR THE MOVEMENT OF RAW MATERIALS, PRODUCT *(Including in-process product)*, PERSONNEL, EQUIPMENT AND WASTE WITHIN THE FACILITY AND BETWEEN LOCATIONS *(If possible).*

II. WATER SYSTEM(S)

A. WHAT TYPES OF WATER SYSTEMS ARE PRESENT IN THE FACILITY? INCLUDE INFORMATION ON THE QUALITY OF INCOMING SOURCE WATER, CONNECTION TO THE SEWER AND BACKFLOW PREVENTION FEATURES.

B. WHAT TYPES OF WATER ARE USED IN PRODUCT MANUFACTURE AND SUPPORT AREAS OF THE FACILITY?

C. DESCRIBE THE PRETREATMENT SYSTEM(S).

D. DESCRIBE THE SYSTEM(S) USED TO PRODUCE PURIFIED WATER.

II. WATER SYSTEM(S) *(Cont'd)*

E. DESCRIBE THE SYSTEM(S) USED TO PRODUCE WATER FOR INJECTION (Include for C, D, and E a schematic drawing of each system instrumentations

F. DESCRIBE THE VALIDATION OF EACH SYSTEM INCLUDING SPECIFICATIONS, SAMPLING LOCATIONS AND FREQUENCY OF MONITORING FOR EACH SYSTEM. INCLUDE DATA SUMMARIES.

G. DESCRIBE THE ROUTINE MONITORING PROGRAM IN PLACE FOR EACH SYSTEM. INCLUDE SPECIFICATIONS, SAMPLING LOCATIONS, AND FREQUENCY AND SUBMIT DATA SUMMARIES FOR RECENT MONITORING.

III. HEATING VENTILATION AND AIR CONDITIONING SYSTEM(S)

A. PROVIDE AN OVERALL DESCRIPTION OF THE HEATING VENTILATION AND AIR CONDITIONING SYSTEM(S) (HVAC) FOR THE MANUFACTURING FACILITY. FOR EACH AIR HANDLING SYSTEM INCLUDE:

1. A NARRATIVE DESCRIPTION. DISCUSS THE COMPOSITION OF THE AIR *(Percent make-up, recirculated or once-through and fan capacity.)*
2. FLOOR DIAGRAM(S) WHICH SHOW THE NUMBER OF AIR HANDLING UNITS AND THE AREA(S) (Rooms) SERVICED BY EACH SYSTEM. THE LOCATION OF AIR RETURN, PRESSURE DIFFERENTIALS, AIR FLOWS, AND ROOM CLASSIFICATION.
3. A REPRESENTATIVE AIR SYSTEM SCHEMATIC WHICH SHOWS THE COMPONENTS AND THEIR PLACEMENT IN THE SYSTEM.

B. DESCRIBE FIRE AND SMOKE CONTROL FEATURES AND ROUTINE CERTIFICATION AND MAINTENANCE PROCEDURES.

C. DESCRIBE VALIDATION OF EACH HVAC SYSTEM(S) INCLUDING SPECIFICATIONS, SAMPLING LOCATIONS AND FREQUENCY OF MONITORING. INCLUDE DATA SUMMARIES.

IV.	RAW MATERIALS AND ANCILLARY FACILITIES
A.	DESCRIBE AREAS AND PROCEDURES FOR RECEIPT OF RAW MATERIALS AND COMPONENTS, INCLUDING SAMPLING, TESTING SEGREGATION AND STORAGE.
B.	DESCRIBE THE RESPONSIBILITY OF THE QUALITY CONTROL/QUALITY ASSURANCE UNIT IN RELATION TO RAW MATERIALS RECEIPT AND TESTING.
C.	ARE ANY RAW MATERIALS TESTED FOR IDENTITY ONLY, AND RELEASED ON A CERTIFICATE OF ANALYSIS FOR OTHER SPECIFICATIONS? IF SO PLEASE LIST THEM.
D.	DESCRIBE AREAS USED FOR STORAGE OF RAW MATERIALS INCLUDING ACCESS AND RESTRICTION OF PERSONNEL TO THESE AREAS.

V.	SOURCE MATERIALS *(i.e., Plasma, ascites for monoclonals, allergens)*
A.	NAME AND ADDRESS OF EACH LOCATION FROM WHICH SOURCE MATERIALS ARE OBTAINED. INCLUDE LICENSE NUMBER IF APPLICABLE.
B.	NAME AND ADDRESS OF EACH LOCATION WHERE PARTIALLY MANUFACTURED SOURCE MATERIAL IS OBTAINED UNDER SHARED MANUFACTURING OR SHORT SUPPLY PROVISIONS. INCLUDE THE LICENSE NUMBER OR MASTER FILE NUMBER IF APPLICABLE AND THE CATEGORY OF COOPERATIVE MANUFACTURING ARRANGEMENT (Shared, short supply).

V. SOURCE MATERIALS *(i.e. Plasma, ascites for monoclonals, allergen(s) (Cont'd)*

C. DESCRIBE PROCEDURES FOR ACCEPTING SOURCE MATERIALS, INCLUDE THE STANDARD OPERATING PROCEDURES (SOP).

D. DESCRIBE AREAS AND PROCEDURES FOR RECEIPT OF SOURCE MATERIALS. INCLUDING SAMPLING. TESTING. SEGREGATION, PERSONNEL RESTRICTIONS AND STORAGE.

I. GENERAL INFORMATION

A. HOST SYSTEMS

1. INDICATE WHERE THE GROWTH, PREPARATION AND STORAGE OF THE MASTER CELL BANK OR SEED AND MANUFACTURER'S WORKING CELL BANK OR SEED TAKE PLACE, INCLUDING MATERIALS OF CONSTRUCTION. *(Include areas where validation was performed on the host system(s)*.

2. DESCRIBE PROCEDURES IN PLACE TO PREVENT CONTAMINATION AND CROSS CONTAMINATION OF THE HOST SYSTEM.

3. DESCRIBE PROCEDURES USED TO TRACK AND ACCOUNT FOR THE MASTER CELL BANK OR SEED AND THE MANUFACTURER'S WORKING CELL BANK OR SEED. INCLUDE A DESCRIPTION OF THE SECURITY PROCEDURES.

4. DESCRIBE FEATURES FOR SEGREGATION OF PRODUCTION WITH SPOREFORMING ORGANISMS FROM THE HOST SYSTEM.

B. INITIAL PROPAGATION

1. DESCRIBE AREAS WHERE THE MANUFACTURER'S WORKING CELL BANK *(MWCB)* OR MANUFACTURER'S WORKING SEED *(MWS)* IS TAKEN FROM STORAGE INTO THE INITIAL GROWTH VESSEL. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS *(Including containment),* GOWNING, ENVIRONMENTAL MONITORING, CLEANING. PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST *(Including the initial growth vessel).*

VI. PROPAGATION OF HOST SYSTEMS *(Cont'd)*

2. DESCRIBE THE METHOD OF TRANSFER AND PROCEDURES USED FOR INITIAL PROPAGATION. INCLUDE INFORMATION ON VALIDATION OF THE TRANSFER PROCEDURES.

C. SCALE-UP

1. DESCRIBE AREAS WHERE TRANSFERS INTO THE SCALE-UP VESSELS TAKE PLACE. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS *(Including containment)*, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST *(Including the scale-up vessels)*.

2. DESCRIBE THE METHOD OF TRANSFER AND PROCEDURES USED FOR SCALE-UP. INCLUDE INFORMATION, ON VALIDATION OF THE TRANSFER PROCEDURES.

3. DESCRIBE IN DETAIL ANY "CLOSED SYSTEMS" USED IN THE TRANSFER PROCESS AND VALIDATION OF THE "CLOSED SYSTEMS"

D. FERMENTATION AND HARVEST

1. DESCRIBE THE AREA WHERE TRANSFER INTO THE FINAL FERMENTATION VESSEL TAKES PLACE. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS *(Including containment)*, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.

2. DESCRIBE THE METHOD OF TRANSFER AND PROCEDURES USED FOR TRANSFER INTO THE FINAL FERMENTATION VESSEL. INCLUDE INFORMATION ON VALIDATION OF THE TRANSFER PROCEDURES.

3. DESCRIBE IN DETAIL ANY "CLOSED SYSTEMS" USED IN THE TRANSFER, AND FERMENTATION PROCESSES AND VALIDATION OF THE "CLOSED SYSTEMS."

VI.	PROPAGATION OF HOST SYSTEMS *(Cont'd)*
4.	DESCRIBE HOW THE ADDITION OF ADDITIVES TO OR THE SAMPLING FROM THE FERMENTATION SYSTEM TAKES PLACE. *(i.e. acids, bases, media, gases, in-process purity checks, etc.)*
5.	DESCRIBE THE EQUIPMENT USED FOR FERMENTATION. INCLUDE MATERIALS OF CONSTRUCTION OF TANKS. VALVES, PORTS, ETC.
6.	DESCRIBE HARVESTING PROCEDURES AND EQUIPMENT. HOW IS THE PRODUCT SEPARATED FROM THE "HOST SYSTEM?"
7.	FOR ALL THE ABOVE PROCEDURES, IF THERE IS ANY INTERMEDIATE STORAGE, DESCRIBE THE CONTAINERS AND AREAS OF THE FACILITY USED FOR STORAGE.
8.	DESCRIBE THE NORMAL MAINTENANCE PROCEDURES AND SCHEDULES.
9.	DESCRIBE THE FLOWS OF CLEAN AND DIRTY MATERIALS.

VII.	INTERMEDIATE PROCESSING
A.	ISOLATION AND PURIFICATION
1.	DESCRIBE THE AREAS USED FOR ISOLATION AND PURIFICATION. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS *(Including containment)*, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.

VII.	INTERMEDIATE PROCESSING *(Cont'd)*
2.	DESCRIBE THE METHOD OF TRANSFER AND PROCEDURES USED FOR THIS STEP. INCLUDE INFORMATION ON VALIDATION OF THE TRANSFER PROCEDURES.
3.	DESCRIBE SPECIAL CHEMICAL PURIFICATION EQUIPMENT SUCH AS COLUMNS, EQUIPMENT USED FOR PRECIPITATION, DIALYSIS AND OTHER CHEMICAL PROCEDURES. DESCRIBE THE PREPARATION SANITIZATION/STERILIZATION AND STORAGE OF THIS EQUIPMENT. INCLUDE ANY APPROPRIATE VALIDATIONS.
4.	DESCRIBE SPECIAL MECHANICAL PURIFICATION EQUIPMENT SUCH AS FILTERS, ULTRACENTRIFUGES, HOMOGENIZERS, ETC. DESCRIBE THE PREPARATION, SANITIZATION/STERILIZATION AND STORAGE OF THIS EQUIPMENT. INCLUDE ANY APPROPRIATE VALIDATIONS.
B.	INACTIVATION
1.	DESCRIBE THE AREAS WHERE INACTIVATION OCCURS. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS *(Including containment)*, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.
2.	DESCRIBE THE METHOD OF ADDITION OF THE INACTIVATING AGENT AND/OR PROCEDURES USED FOR THIS STEP. INCLUDE INFORMATION ON VALIDATION OF THE TRANSFER PROCEDURES.
3.	DESCRIBE THE CONTAINERS AND AREAS USED FOR STORAGE OF PRODUCT DURING AND AFTER INACTIVATION. INCLUDE SPECIFIC INFORMATION ON SEGREGATION FROM NON-INACTIVATED PRODUCT DURING STORAGE.
C.	ADDITIONAL PROCESSING
1.	DESCRIBE THE AREAS WHERE ADDITIONAL PROCESSING SUCH AS ADDITION OF ADJUVANTS, PRESERVATIVES, CONJUGATION, POOLING OF BULK CONCENTRATES, ETC. OCCUR. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS *(Including containment)*, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.

VII. INTERMEDIATE PROCESSING *(Cont'd)*

2. DESCRIBE THE METHODS USED TO CONDUCT THE ADDITIONAL PROCESSING. *(Example: How is adjuvant or preservative added? Is this an aseptic process?)*

3. DESCRIBE CONTAINERS AND AREAS USED FOR STORAGE OF IN-PROCESS PRODUCT.

VIII. FORMULATION AND FINAL PRODUCT PREPARATION

A. FINAL BULK

1. DESCRIBE AREAS, PROCEDURES AND EQUIPMENT FORMULATION OF THE FINAL BULK. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.

2. DESCRIBE THE CONTAINERS AND AREAS USED FOR STORAGE OF INTERMEDIATE *(Presterilized final bulk)* PRODUCT.

B. STERILIZATION OF THE FINAL BULK

1. DESCRIBE AREAS, PROCEDURES AND EQUIPMENT USED FOR STERILIZATION OF THE FINAL BULK. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS. GOWNING. ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.

2. DESCRIBE THE CONTAINER AND AREAS USED FOR STORAGE OF FINAL STERILIZED BULK PRODUCT.

C. FILLING

1. DESCRIBE AREAS, PROCEDURES AND EQUIPMENT USED FOR FILLING OF THE FINAL CONTAINERS. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.

2. DESCRIBE MEDIA FILL VALIDATION. INCLUDE DATA SUMMARIES.

D. LYOPHILIZATION

DESCRIBE AREAS, PROCEDURES AND EQUIPMENT FOR LYOPHILIZATION OF THE FINAL CONTAINERS. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST. VALIDATION SHOULD BE DESCRIBED IN THE VALIDATION SECTION. IF FILLED, PARTIALLY STOPPERED CONTAINERS ARE TRANSPORTED TO A SEPARATE AREA FOR LYOPHILIZATION, DESCRIBE TRANSFER PROCEDURES IN DETAIL.

E. *IN VITRO* DIAGNOSTICS

DESCRIBE AREAS, PROCEDURES AND EQUIPMENT FOR FINISHING OF *IN VITRO* DIAGNOSTIC PRODUCT *(e.g. Plate coating and drying bead coating etc.)* THAT ARE NOT COVERED IN OTHER SECTIONS OF THIS APPLICATION. INCLUDE A DESCRIPTION OF THE FOLLOWING: ROOM AIR SUPPLY, TEMPERATURE AND HUMIDITY; MATERIALS OF CONSTRUCTION AND ROOM SURFACES; ROOM CLASSIFICATION, ENVIRONMENTAL MONITORING AND PERSONNEL GOWNING; CLEANING PROCEDURES; PRODUCT CHANGEOVER PROCEDURES; EQUIPMENT LIST.

F. CAPPING

1. DESCRIBE THE AREAS AND EQUIPMENT USED FOR CAPPING OF THE FINAL CONTAINERS, INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.

2. IF UNLABELED VIALS ARE STORED BEFORE LABELING, DESCRIBE THE AREAS AND PROCEDURES USED TO STORE THE PRODUCT.

G. PACKAGING AND LABELING

1. DESCRIBE THE AREAS AND EQUIPMENT USED FOR LABELING AND PACKAGING OF FINAL CONTAINERS. HOW IS PHYSICAL SEPARATION ACCOMPLISHED? WHAT PROCEDURES ARE IN PLACE TO PREVENT MIX-UPS OR MISLABELING OF FINAL PRODUCT?

VIII.	FORMULATION AND FINAL PRODUCT PREPARATION *(Cont'd)*
2.	INDICATE WHERE LABELING IS STORED AND HOW ACCESSIBILITY TO THE AREA IS CONTROLLED.
3.	DESCRIBE THE LABELING RECONCILIATION PROCEDURE.
4.	DESCRIBE AREAS USED TO STORE FINAL LABELED PRODUCT. INCLUDE INFORMATION ON SEGREGATION OF RELEASED AND UNRELEASED PRODUCT.

IX.	COMPUTER SYSTEMS
A.	DESCRIBE ALL PROCESSING STEPS WHICH ARE COMPUTER CONTROLLED. DESCRIBE EACH SYSTEM USED IN THESE STEPS. INCLUDE A SCHEMATIC DIAGRAM OF THE SYSTEM AND THE FUNCTIONAL STATEMENT.
B.	DESCRIBE ANY COMPUTER SYSTEM USED TO CONTROL THE TRACKING AND/OR STATUS OF RAW MATERIALS, IN-PROCESS MATERIALS, OR FINAL PRODUCT.
C.	DESCRIBE THE VALIDATION AND SECURITY OF THE HARDWARE AND SOFTWARE OF EACH SYSTEM.
D.	INDICATE WHERE THE SOFTWARE WAS DEVELOPED AND DESCRIBE PROCEDURES FOR PROGRAM UPDATES.

X. SUPPORT AREAS

A. DESCRIBE THE AREAS AND EQUIPMENT USED FOR MEDIA AND BUFFER PREPARATION. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGEOVER PROCEDURES AND EQUIPMENT LIST.

B. DESCRIBE THE AREAS USED FOR CLEANING OF EQUIPMENT. INCLUDE A DESCRIPTION OF THE ROOM AIR SUPPLY, ROOM SURFACES, MATERIALS OF CONSTRUCTION, ROOM CLASS, GOWNING, ENVIRONMENTAL MONITORING, CLEANING, PRODUCT CHANGE-OVER PROCEDURES AND EQUIPMENT LIST.

C. DESCRIBE MAINTENANCE AND SERVICE AREAS OF THE FACILITY.

D. DESCRIBE THE WASTE HANDLING AND DISPOSAL SYSTEMS FOR THE FACILITY. DO DECONTAMINATION AND STERILIZATION TAKE PLACE IN THE SAME AREA? IF SO, PLEASE DESCRIBE PROCEDURES TO PREVENT MIXUPS.

E. DESCRIBE THE AREAS USED FOR STERILIZATION AND DEPYROGENATION OF EQUIPMENT AND FINAL CONTAINER COMPONENTS.

F. DESCRIBE AREAS USED FOR STORAGE OF IN-PROCESS MATERIALS AND FINAL PRODUCT *(Or refer back to appropriate section if already included).*

XI. QUALITY CONTROL AREAS

A. DEFINE THE QUALITY CONTROL UNIT AND HOW ITS REPORTING STRUCTURE RELATES TO THE REST OF THE ORGANIZATION. *(An organizational chart may be used.)* WHAT IS THE RELATIONSHIP BETWEEN QUALITY CONTROL (QC) AND QUALITY ASSURANCE (QA)?

XI. QUALITY CONTROL AREAS *(Cont'd)*

B. DESCRIBE THE FACILITIES WHERE TESTING *(Including off-site or contract testing)* ARE PERFORMED. INCLUDE A COPY OF THE WRITTEN AGREEMENT WITH ANY CONTRACT TESTING SITE. *(For animal testing refer to the animal facilities section).*

C. DESCRIBE THE SEPARATION OF FUNCTIONS USING MICROORGANISMS. DESCRIBE THE STORAGE OF SAMPLES AND STANDARDS. DESCRIBE THE CALIBRATION AND MAINTENANCE OF EQUIPMENT.

D. LIST MAJOR EQUIPMENT USED IN QC TESTING OF THE PRODUCT.

E. FOR STERILITY TEST AREAS, DESCRIBE THE PRECAUTIONS TAKEN TO PREVENT FALSE POSITIVES FROM OCCURRING.

XII. ANIMAL FACILITIES FOR TESTING

A. WHAT ANIMALS ARE USED IN THE TESTING OF PRODUCT(S). INCLUDE THE TYPES OF ANIMALS AND HOW THEY ARE USED FOR EACH SPECIFIC PRODUCT. INCLUDE NUMBER OF ANIMALS AND NUMBER OF ANIMALS PER CAGE. IS THERE A SENTINEL ANIMAL PROGRAM IN PLACE?

B. GIVE THE ADDRESS OF LOCATIONS AND OUTLINE THE FOLLOWING FEATURES OF ALL ANIMAL FACILITIES USED IN TESTING.

1. HVAC SYSTEM
2. WATER SYSTEM
3. MATERIALS OF CONSTRUCTION
4. FLOW OF MATERIALS AND ANIMALS
5. RELATIONSHIP TO OTHER MANUFACTURING AREAS
6. SEGREGATION PROCEDURES FOR MULTI-PRODUCT AREAS
7. SUPPORT AREAS FOR CAGE WASHING, FOOD HANDLING, ETC.

C. DESCRIBE ANIMAL QUARANTINE PROCEDURES.

XII. ANIMAL FACILITIES FOR TESTING *(Cont'd)*

D. DO THE SAME PERSONNEL WORK IN ANIMAL AND MANUFACTURING AREAS ON THE SAME DAY? DESCRIBE SPECIAL PERSONNEL PRACTICES AND GOWNING FOR THE ANIMAL FACILITY. PLEASE PROVIDE A PERSONNEL FLOW DIAGRAM.

XIII. ANIMAL FACILITIES FOR PRODUCTION

A. WHAT ANIMALS ARE USED IN MANUFACTURING OF PRODUCTS? INCLUDE THE TYPES OF ANIMALS AND HOW THEY ARE USED FOR EACH SPECIFIC PRODUCT. INCLUDE NUMBER OF ANIMALS USED AND NUMBER OF ANIMALS PER CAGE. IS THERE A SENTINEL ANIMAL PROGRAM IN PLACE?

B. GIVE THE ADDRESSES OF LOCATIONS AND OUTLINE THE FOLLOWING FEATURES OF ALL ANIMAL FACILITIES USED IN MANUFACTURE.

1. HVAC SYSTEM
2. WATER SYSTEM
3. MATERIALS OF CONSTRUCTION
4. FLOW OF MATERIALS AND ANIMALS
5. RELATIONSHIP TO OTHER MANUFACTURING AREAS
6. SEGREGATION PROCEDURES FOR MULTI-PRODUCT AREAS
7. SUPPORT AREAS FOR CAGE WASHING, FOOD HANDLING, ETC.

C. ANIMAL SOURCE

ARE ANIMALS BRED ON-SITE OR ARE THEY RECEIVED FROM ANOTHER BREEDING FACILITY? IF RECEIVED FROM ANOTHER FACILITY, DESCRIBE PROCEDURES FOR RECEIPT OF ANIMALS.

D. DESCRIBE ANIMAL QUARANTINE PROCEDURES.

E. ANIMAL HEALTH

1. DESCRIBE VETERINARY CARE, INCLUDING ROUTINE TESTING AND DIAGNOSTIC ANALYSIS PROVIDED BY VETERINARY PERSONNEL AND FREQUENCY OF ANIMAL SITE VISITS.

2. WHO OBSERVES THE ANIMALS ON A DAILY BASIS FOR GENERAL HEALTH DURING QUARANTINE AND PRODUCTION PERIODS?

XIII.	ANIMAL FACILITIES FOR PRODUCTION *(Cont'd)*

F. EQUIPMENT/FACILITIES

1. DESCRIBE CLEANING PROCEDURES INCLUDING FREQUENCIES FOR CAGES, WATER BOTTLES, SIPPERS, ETC. HOW OFTEN IS BEDDING CHANGED?

2. DESCRIBE ANIMAL ROOM CLEANING PROCEDURES. WHERE ARE ANIMALS HOUSED DURING CLEANING?

3. WHAT IS THE METHOD OF FEED PASTEURIZATION? HOW WAS THIS PROCEDURE VALIDATED?

4. DESCRIBE FEED AND WATERING PROCEDURES/DEVICES.

G. PROCEDURES

1. DESCRIBE THE AREAS AND ENVIRONMENTAL CONDITIONS FOR PRIMING, INOCULATION, TAPPING, POOLING AND PROCESSING PROCEDURES WHICH TAKE PLACE IN ANIMAL PRODUCTION AREAS.

2. HOW ARE ANIMAL CAGES LABELED?

3. DESCRIBE ANY CONTAINERS OR EQUIPMENT USED DURING PRODUCTION.

H. PERSONNEL

1. DESCRIBE THE ANIMAL TECHNICIAN TRAINING PROGRAM.

XIII. ANIMAL FACILITIES FOR PRODUCTION *(Cont'd)*

2. DO THE SAME PERSONNEL WORK IN ANIMAL AND MANUFACTURING AREAS ON THE SAME DAY?

3. DESCRIBE SPECIAL PERSONNEL PRACTICES AND GOWNING FOR THE ANIMAL FACILITY. PLEASE PROVIDE A PERSONNEL FLOW DIAGRAM.

XIV. CALIBRATION AND VALIDATION

A. FOR ALL MAJOR SYSTEMS *(Except those where validation has been previously described in another section)* SUCH AS WASTE DISPOSAL, CLEAN-IN-PLACE (CIP), STEAM-IN-PLACE (SIP), COMPRESSED AIR, ETC., PLEASE PROVIDE A DESCRIPTION OF THE VALIDATION STUDIES PERFORMED INCLUDING THE RESULTS. INCLUDE A TABLE OF ALL VALIDATIONS DONE AND THE RELATED PROTOCOLS AND A SUMMARY OF THE RESULTS FOR EACH MAJOR SYSTEM. INCLUDE:
   1. INSTALLATION QUALIFICATION
   2. OPERATION QUALIFICATION
   3. PERFORMANCE QUALIFICATION
   4. REVALIDATION

B. FOR MAJOR PIECES OF EQUIPMENT *(Autoclaves, dry heat ovens, lyophilizers, hoods, etc; reference chromatography columns to Product License Application (PLA) if appropriate)* PLEASE PROVIDE A DESCRIPTION OF THE VALIDATION STUDIES PERFORMED INCLUDING THE RESULTS. INCLUDE A TABLE OF ALL VALIDATIONS DONE AND THE RELATED PROTOCOLS AND A SUMMARY OF THE RESULTS FOR EACH PIECE OF EQUIPMENT. INCLUDE:
   1. INSTALLATION QUALIFICATION
   2. OPERATION QUALIFICATION
   3. PERFORMANCE QUALIFICATION
   4. REVALIDATION

C. FOR CRITICAL PROCESSES SUCH AS CLEANING OF PRODUCT CONTACT PARTS AND MAJOR EQUIPMENT IN PRODUCT CONTACT, DISINFECTION, PRODUCT CHANGEOVER, ETC., PLEASE DESCRIBE THE VALIDATION STUDIES THAT WERE PERFORMED AND RESULTS OF EACH.

XV. RECORDS

A. DESCRIBE THE RELATIONSHIP BETWEEN THE MASTER PRODUCTION RECORD AND EACH BATCH PRODUCTION RECORD.

B. EXPLAIN PREPARATION OF RECORDS AND SIGN OFF AUTHORITY WITHIN THE ORGANIZATION.

XV. RECORDS *(Cont'd)*

C. HOW ARE RECORDS ASSEMBLED, STORED AND ACCESSED?

D. WHO REVIEWS THE RECORDS FOR EACH LOT PRIOR TO RELEASE OF THE LOT? DESCRIBE THE METHOD OF DOCUMENTING SUCH REVIEWS.

E. HOW LONG ARE RECORDS KEPT?

F. DESCRIBE THE RECORDS USED FOR DISTRIBUTION. HOW DO THESE RECORDS ALLOW FOR EFFICIENT RECALL?

G. DESCRIBE THE COMPLAINT FILE AND ADVERSE REACTION REPORTING PROCEDURES.

H. DESCRIBE AUDIT PROCEDURES AND WHEN AND HOW TREND ANALYSES ARE PERFORMED.

XVI. ADDITIONAL INFORMATION REQUIRED TO BE SUBMITTED

A. PLEASE PROVIDE THE FOLLOWING ADDITIONAL INFORMATION:

1. A DESCRIPTION OF THE LOT NUMBERING SYSTEM.
2. AN ORGANIZATIONAL CHART.
3. AN ENVIRONMENTAL ASSESSMENT REPORT.
4. WRITTEN AGREEMENTS *(If not submitted in any other section)*
5. CURRICULUM VITAE FOR KEY MANUFACTURING AND RESPONSIBLE PERSONNEL.
6. AN OVERVIEW OF THE GMP TRAINING PROGRAM.

XVII. COMMENTS

XVII. NAMES AND TITLES OF EXPERTS RESPONSIBLE FOR THE PRODUCTION AND TESTING OF PRODUCT

TITLE	TYPED NAME	SIGNATURE

CERTIFICATION

I certify that all statements made in the application are true and correct to the best of my knowledge and ability. I am familiar with the pertinent Sections of Title 21, Code of Federal Regulations, and am aware of my responsibilities described therein.

WARNING: A willfully false certification is a criminal offense, U.S. Code, Title 18, Section 1001.

SIGNATURE OF RESPONSIBLE HEAD	TYPED NAME AND TITLE	DATE